

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

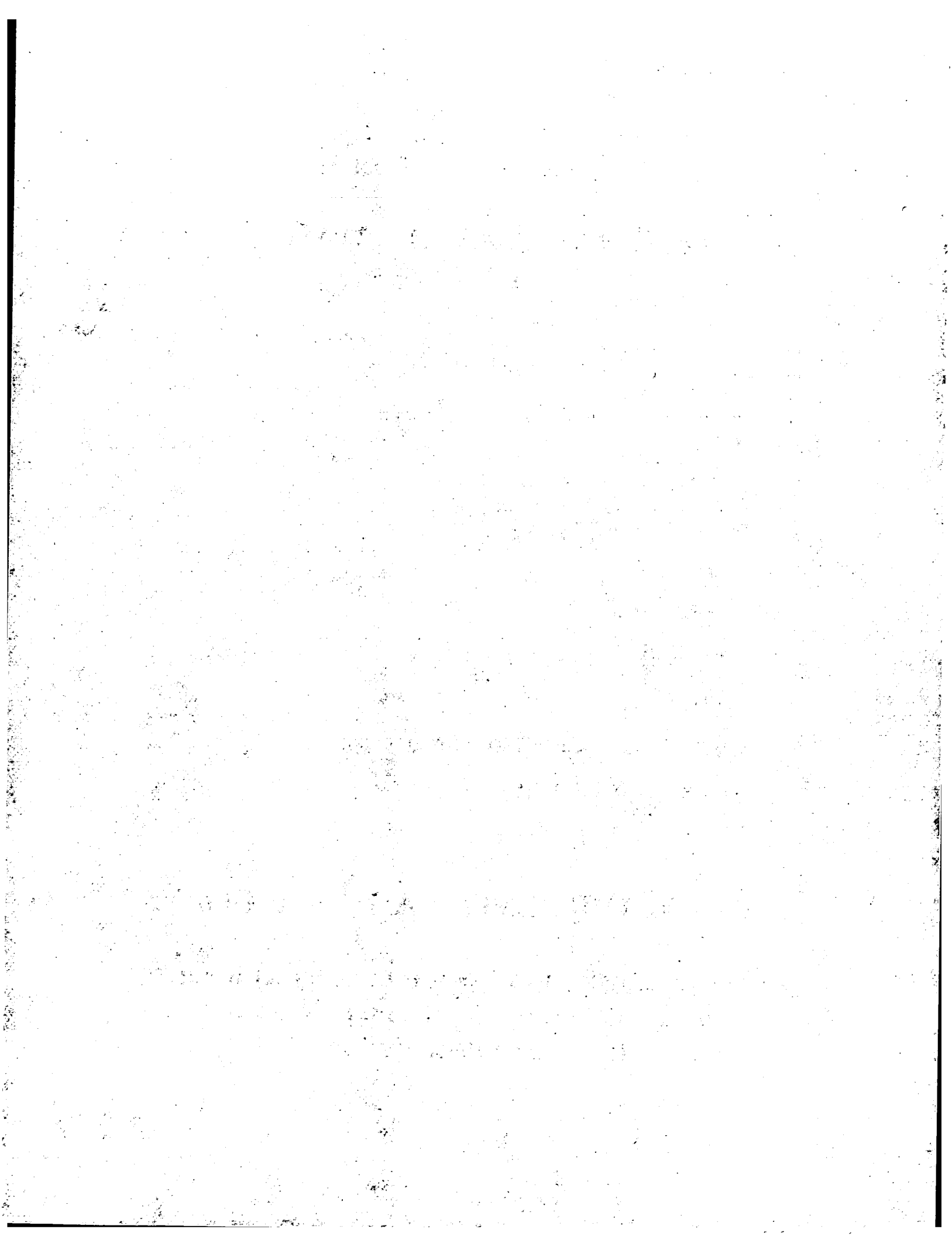
Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**





INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : G01N 33/558, 33/543	A1	(11) International Publication Number: WO 00/20866 (43) International Publication Date: 13 April 2000 (13.04.00)
(21) International Application Number: PCT/GB99/03249 (22) International Filing Date: 1 October 1999 (01.10.99) (30) Priority Data: 9821526.2 2 October 1998 (02.10.98) GB (71) Applicant (for all designated States except US): GENOSIS LIMITED [GB/GB]; 12-50 Kingsgate Road, Kingston-Upon-Thames KT2 5AA (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BARRADINE, Martin [GB/GB]; Genosis Limited, 12-50 Kingsgate Road, Kingston-Upon-Thames KT2 5AA (GB). GURMIN, Tracey [GB/GB]; Genosis Limited, 12-50 Kingsgate Road, Kingston-Upon-Thames KT2 5AA (GB). (74) Agent: FISHER, Adrian, John; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: ASSAY USING POROSITY-REDUCTION TO INHIBIT MIGRATION <div data-bbox="423 1184 1354 1360" data-label="Image"> </div> (57) Abstract <p>Device for assaying an analyte, comprising a labelling zone, where a label can bind to the analyte, in communication with a capture zone, wherein the pore size of the capture zone is such that label which is not bound to the analyte can migrate therethrough, whereas label which is bound to the analyte cannot. During migration from the labelling zone (large pore size) to the capture zone (small pore size), unbound label can pass into and through the capture zone, whereas bound label will be captured at the junction of the labelling zone and the capture zone. The device relies upon the label being smaller than the analyte, such that free label is not retarded by the capture zone. It is particularly suitable for assaying analytes such as spermatozoa, which are large in comparison with a label such as a labelled antibody.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

ASSAY USING POROSITY-REDUCTION TO INHIBIT MIGRATION

Technical field

This invention relates to assay devices for measuring analytes. In particular, it relates to devices which capture analytes mechanically within a porous material, rather than using
5 conventional immuno-capture techniques.

Background Art

The format of the standard rapid test lateral flow device has remained unchanged for around ten years. Typically, the device will comprise a nitrocellulose strip. Sample is applied to an application zone, from which it flows by capillary action through a zone containing a
10 visibly-labelled antibody specific for the analyte in question. Free and bound label continue to migrate to a capture zone, where immobilised antibody specific for the analyte binds the analyte-label complex. Free label (unbound antibody) continues to migrate, leaving an analyte-specific signal in the capture zone. These types of lateral flow device are disclosed in, for example, EP-A-0284232. Numerous variations to the basic assay have been described,
15 including those in WO92/12428, EP-A-0613005, WO97/06439, and US-5,741,662.

In all cases, however, capture of the analyte-label complex is mediated by an immobilised reagent, which is typically an antibody that is specific for the analyte. This is unsatisfactory in many respects.

Firstly, manufacturing quality control is difficult. The solid phase capture membrane is
20 typically made from nitrocellulose, and antibodies are applied to the membrane directly. Nitrocellulose manufacture is not, however, homogeneous. Quality control of the solid phase antibody is therefore limited to testing a statistical sample of devices from the same, but heterogeneous, batch, and assuming that the whole batch will perform within specific tolerances. It is well known, however, that membranes vary considerably, even within a single
25 batch or lot number.

Secondly, they are relatively cumbersome to manufacture. The application of immobilised antibody to the strip requires a separate step from the application of the mobile labelled antibody. The capture antibody can be sprayed directly onto the nitrocellulose strip, but the label antibody has to be soaked into material which is subsequently attached to the
30 nitrocellulose strip, with an overlap to ensure capillary flow.

Thirdly, antibody is immobilised by spraying a solution onto a membrane. Some of the antibody does not bind to the membrane strongly, however, and some remains loosely associated with immobilised antibody. This semi-bound or unbound antibody can become mobile when the solvent front passes over it, resulting in lower binding of label at the detection zone. If the device includes a control line, this will capture the additional label which should have been captured at the detection zone. Tests that rely on a comparison of colour intensity between control and detection lines, such as ovulation prediction kits, may therefore give false results. Furthermore, application by spraying inevitably leads to diffusion into the membrane, leading to a more diffuse and less focused detection signal.

Fourthly, the sensitivity of the devices is limited by their format. Analyte and labelled-antibody react as they migrate through the membrane, and flow rates are therefore adjusted to enable the labelled-antibody to flow at the solvent front in order to maximise the amount of time in which the analyte-label complex can form. The complex passes over the capture antibody for a short time, however, thus imposing constraints on the design of the test and its performance characteristics. The short reaction time decreases sensitivity, and also means that high affinity capture antibodies are required.

Finally, the shelf-life of these test devices is often limited by the collapse of the immobilised capture antibody onto the membrane over time.

These shortcomings in the prior art devices are addressed by the present invention, which does not use immobilised antibody to capture an analyte-label complex.

Disclosure of the invention

The invention provides a device for assaying an analyte, comprising a labelling zone, where a label can bind to the analyte, in communication with a capture zone, wherein the pore size of the capture zone is such that label which is not bound to the analyte can migrate therethrough, whereas label which is bound to the analyte cannot.

During migration from the labelling zone to the capture zone, unbound label can pass into and through the capture zone, whereas bound label will be captured at the junction of the labelling zone and the capture zone. A comparison of the amount of label captured at the entrance to the capture zone with the amount migrating through the capture zone allows the level of analyte to

be assessed – as analyte concentration increases, the amount of label retained at the junction of the labelling zone and the capture zone also increases.

It will be apparent that the invention relies upon the label being smaller than the analyte, such that free label is not retarded by the capture zone.

- 5 The device is particularly suitable for assaying analytes such as biological cells, which are large in comparison with a label such as a labelled antibody. Preferred cells for assay are spermatozoa and micro-organisms, such as bacteria.

The labelling zone is where label comes into contact with the analyte. It is preferably formed from fibrous material, such as a pad of HDPE material, bonded polyester fibre, glass fibre, or
10 the like. The pore size should be large enough to allow the analyte to move relatively freely, in contrast to the pore size of the capture zone.

The label is typically an antibody which can bind to the analyte of interest, and which has been suitably labelled. The label is preferably visible to the naked eye *eg.* a fluorescent label, or a particulate label such as colloidal gold (which is visible as a pink colour), or a stain such as
15 eosin. It will be appreciated that the term 'antibody' may include polyclonal and monoclonal antibodies, as well as antibody fragments (*eg.* $F(ab)_2$, Fc *etc.*), provided that the necessary biological specificity is retained.

The capture zone can be made from any suitable porous material through which unbound label can migrate, whilst analyte-bound label cannot. This requirement is reflected in the pore size of
20 the capture zone. In one embodiment, the capture zone will be made from HDPR with a nominal pore size of around 1-75 μ m, preferably 10-50 μ m, and more preferably 20-35 μ m. In second embodiment, the capture zone will be made from nitrocellulose, with a nominal pore size of around 1-15 μ m, preferably 3-10 μ m, and more preferably 5-8 μ m.

In some embodiments, the labelling zone and capture zone may be formed from a single piece
25 of porous material, which contains a region of reduced pore size. By crushing or compressing a region of a porous material, for instance, the pore size can be reduced such that an analyte-bound label cannot enter the compressed region *ie.* to form a capture zone. As an alternative, the pores of the material could be partially blocked, to achieve the same effect.

As is well known to those in the art, the nominal pore size of a porous material can be
30 determined by hard particle challenge testing *ie.* by determining the maximum diameter of

spherical particles which can pass through the material. Alternatively, the pore size of a material may be determined by measuring its 'bubble point'. The bubble point is the pressure required to force air through a (water) wet membrane, and correlates with the pore size as measured by particle retention (although at extremes of pressure and pore size, the correlation may be weaker). The bubble point is generally easier to measure than particle retention and is thus the preferred test when assessing pore size.

When the device of the present invention is to be used for detecting and measuring a motile analyte in particular (such as motile spermatozoa or motile bacteria), the appropriate pore size may be determined empirically by routine testing.

- 10 In preferred embodiments, the capture zone includes a region which retains label which is not bound to the analyte (a 'label control' region). This will typically comprise antibody fixed within the capture zone which can bind to the analyte-specific label. Label which passes through the capture zone, rather than being captured on entry thereto, is thus retained within the 'label control' region, where it can be measured. If the analyte-specific label is a murine
15 monoclonal antibody, for instance, then the capture zone may include a region containing immobilised anti-mouse antibody. Unbound label is thus retained either at the junction of the labelling zone and the capture zone or at the 'label control' region. A comparison of the amount of label in these two positions allows the amount of analyte in the original sample to be assessed.
- 20 In an alternative arrangement, the device might utilise two separate labelled antibodies in the labelling zone, only one being analyte-specific. The label which does not recognise the analyte is instead specific for the antibody in the 'label control' region. This label passes through the capture zone and is retained at the 'label control' region, giving a standard for comparison with the analyte-specific signal at the entrance to the capture zone; the analyte-specific label does
25 not bind the 'label control' antibody, and continues to migrate.

The interface between the labelling zone and the capture zone is preferably narrow compared to the length of the capture zone. Where the labelling zone and the capture zone are formed from strips of overlapping material, a narrow interface between them can be achieved by the presence of a non-porous material covering the majority of the overlap. By ensuring that the
30 interface between the labelling zone and the capture zone is narrow, the analyte-label complex is focused at the junction of the labelling zone and the capture zone, giving a sharper signal.

The analyte is preferably spermatozoa. The label preferably recognises a surface antigen which is present on the majority of a population of spermatozoa, rather than a subset. Whilst any surface antigen may be used, therefore (eg. P34H (WO97/40836), SP-10 (WO95/29188), see also EP-A-0387873), 'universal' antigens such as CD59 are preferably used. It will be appreciated that, where the antigen is not sperm-specific (ie. it is also present on other cell types, such as CD59), the sample being analysed may require treatment to remove non-spermatozoa cells. The capture zone for retarding the migration of spermatozoa is preferably a nitrocellulose membrane with a nominal pore size in the region of 5µm – 8µm. A sperm sample may be treated to separate motile and non-motile cells before analysis (eg. see international patent applications PCT/GB99/01929 and PCT/GB99/02685). The device of the invention can be used to determine the relative numbers of motile and non-motile cells in a given sample by comparing results after such a separation. The device of the invention may comprise means to separate motile spermatozoa from non-motile spermatozoa before entry to the capture zone such that, after operation, three signals are apparent – one where label has bound non-motile cells, one where label has bound motile cells, and one of free label. It is not always necessary to separate cells in this way, however eg. in vasectomy verification, a test can simply indicate overall levels of spermatozoa, motile or not. Typically, the sperm-containing sample to be analysed will not be 'neat' semen, but will be diluted, and possibly treated to remove non-spermatozoa cells. If 'neat' semen is analysed, it will generally be necessary to use a sperm-specific label, so that non-spermatozoa cells are not labelled.

As an alternative, the analyte may be a micro-organism. The micro-organism might be a bacterium, such as enterotoxigenic *E.coli* ('ETEC') [eg. see Levine (1987) *J. Infect. Dis* 155:377-289], for which any suitably-labelled ETEC-specific antibody can be used as the label eg. gold-conjugated anti-CFA/I monoclonals. The micro-organism might be a yeast, such as *Candida*.

In preferred embodiments, migration of a sample to the capture zone is assisted by a wick before the labelling zone and/or a wick after the capture zone, to aid capillary movement.

In some embodiments of the invention, a sample might be applied directly to the capture zone. In this arrangement, label will migrate from the labelling zone through the capture zone, in which the sample is encountered. Label will be retained by analyte which has been retarded in the capture zone, and unbound label will continue to migrate.

The device of the invention can be produced simply and cheaply, conveniently in the form of a test strip or dipstick. Furthermore, it can be used very easily, for instance by the home user. The invention thus provides an assay device which can be used at home as a basic screen of, for instance, male fertility.

5 Brief description of drawings

Figure 1 shows a lateral flow device according to the invention, and Figure 2 shows the results of a dose-response curve experiment using this device.

Modes for carrying out the invention

Example 1 - a basic lateral flow test device

- 10 The device shown in Figure 1 comprises a strip of filter paper (1), a first absorbent pad (2) containing gold-labelled anti-spermatozoa labelling antibody, a second absorbent pad (3) for receiving a sperm-containing sample, a nitrocellulose membrane (4), and an upper wick (5). Between the absorbent pad (3) and the nitrocellulose membrane (4) is a thin acetate strip (6) which prevents contact between the pad (3) and membrane (4) except for a narrow margin (7).
- 15 Membrane (4) includes a line (8) of immobilised antibody which can react with unbound anti-sperm labelling antibody.

The nitrocellulose membrane (4) measures 5mm x 25mm, and is mounted on a stiff plastic backing measuring 5mm x 73mm. At one end of the membrane (4), upper wick (5), measuring 5mm x 30mm, is attached such that they overlap by 5mm, and at the other end a thin acetate

20 strip (6) measuring 5mm x 4mm is affixed. Absorbent pad (3), measuring 5mm x 5mm is placed over acetate strip (6), such that it contacts the nitrocellulose strip (4) with a 5mm x 1mm margin. Absorbent pad (2), measuring 5mm x 5mm, is attached such that it abuts both pad (3) and strip (6); filter paper (1), measuring 20mm x 5mm is attached so that it overlaps by 2mm beneath absorbent pad (2).

- 25 Filter paper (1) is Ahlstrom blotting grade paper number 222. Absorbent pad (2) is HDPE conjugate material, thickness 0.6mm, nominal pore size 99µm (Sintair Ltd, England). This was saturated with a solution of monoclonal anti-CD59 antibody (Bristol University, UK) conjugated to 40nm gold particles (diluted in purified water containing 5% trehalose, 0.1% Triton-X (Sigma) and 1% BSA) and then dried completely under vacuum. Absorbent pad (3) is
- 30 made from the same HDPE material, but was saturated with 1% BSA and 0.1% Triton-X at pH

6.6, and then dried. The nitrocellulose membrane (4) is an Advanced MicroDevices 8µm nitrocellulose membrane (CNPf-S1-L2-H50, lot number HF322228/731). Upper wick (5) is formed from Whatman chromatography paper (catalogue number 3MM CHR, lot number 3030640), left untreated as supplied.

- 5 A thin line (8) of control antibody [Jackson's AffiniPure goat anti-mouse IgG, FC and fragment specific (minimum cross-reaction with human, bovine and horse serum proteins; code 115-005-071, lot 36019), diluted to 0.02mg/ml in 2mM phosphate and 0.017% BSA] was immobilised on membrane (4) between the margin (7) and upper wick (5).

To use the device, a sperm-containing specimen is applied to absorbent pad (3), and filter paper
10 (1) is placed in an appropriate buffer or the like. The buffer migrates through filter paper (1) and absorbent pad (2), bringing the gold-conjugated antibody into contact with any spermatozoa in pad (3). As the solution migrates through pad (3), towards margin (7), the antibody can bind to the sample. Labelled spermatozoa cannot pass through the nitrocellulose membrane (4), due to its small pore size, so are instead retarded around margin (7). Margin (7)
15 thus serves as a 'choking zone' which captures material which is too large to pass through the pores of membrane (4). Unbound gold-conjugated antibody, however, will continue to migrate through the membrane until it reaches antibody line (8), which binds gold-conjugated antibody. At this stage, therefore, there may be two lines visible – one at the 'choking zone' (7), where migration of the label has been retarded by binding to spermatozoa, and one at line (8), where
20 migration has been retarded by binding to the immobilised control antibody.

Example 2 – qualitative sperm testing

In a test experiment, two samples were tested – the first was a sample of motile spermatozoa in HEPES buffer (obtained by indirect swim up from the ejaculate of a fertile man), and the second was just HEPES buffer. 75µl of each sample was placed on the absorbent pad (3) of
25 two separate devices, and these were placed in separate wells, each containing 75µl HEPES.

After 15 minutes, the device used with the first sample had developed two clear red lines on membrane (4), the first about 1mm above the absorbent pad (3), the second at line (8). The other device, however, contained a single red line at line (8). The device is thus able to capture spermatozoa mechanically around the 'choking zone'.

Example 3 – quantitative sperm testing

In a further experiment, a sample of motile spermatozoa in HEPES buffer was obtained by indirect swim up from the ejaculate of a fertile man. The number of motile sperm per ml in the HEPES portion of the swim up was established using a counting chamber and found to be 3.5 million. This sample was diluted with HEPES to give four further samples with 2, 1, 0.5 and 0.25 million sperm per ml respectively. 75µl of each of these five samples were placed on the absorbent pads (3) of five separate devices and these were placed in separate wells containing 75µl HEPES. Buffer alone was used as a control.

After 15 minutes, each of the devices had developed two clear red lines on membrane (4), the first about 1mm above the absorbent pad (3), the second at line (8). As clearly shown in Figure 2, however, the intensity of the first line decreased as the number of spermatozoa in the sample decreased by dilution. No first line was visible on the control. The device is thus able to demonstrate a dose response capture around the 'choking zone'.

Further embodiments

It will be understood that the invention is described above by way of example only and modifications may be made whilst remaining within the scope and spirit of the invention.

CLAIMS

1. A device for assaying an analyte comprising a labelling zone, where a label can bind to the analyte, in communication with a capture zone, wherein the pore size of the capture zone is such that label which is not bound to the analyte can migrate therethrough, whereas label
5 which is bound to the analyte cannot.
2. A device according to claim 1, wherein the label is an antibody which can bind to the analyte of interest.
3. A device according to claim 2, wherein the label is visible to the naked eye.
4. A device according to claim 3, wherein the label is colloidal gold.
- 10 5. A device according to any preceding claim, wherein the capture zone is nitrocellulose.
6. A device according to any preceding claim, wherein the labelling zone and capture zones are formed from a single piece of porous material which contains a region of reduced pore size.
7. A device according to any preceding claim, wherein the capture zone includes a region
15 which retains label which is not bound to the analyte.
8. A device according to any preceding claim, wherein the interface between the labelling zone and the capture zone is narrow compared to the length of the capture zone.
9. A device according to any preceding claim, wherein the analyte is spermatozoa.
10. A device according to claim 10, wherein the label recognises CD59.
- 20 11. A device according to any one of claims 1 to 8, wherein the analyte is a micro-organism.
12. A device according to any preceding claim, wherein migration of a sample to the capture zone is assisted by a wick before the labelling zone and/or a wick after the capture zone
13. A device according to any preceding claim, in the form of a test strip or a dipstick.

1/2

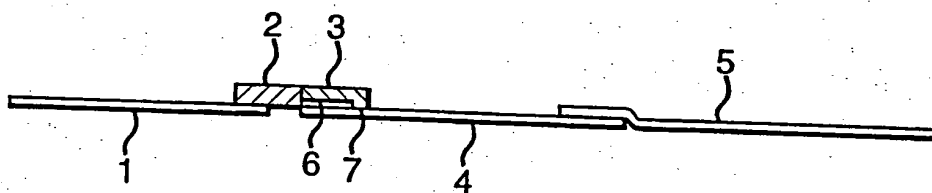
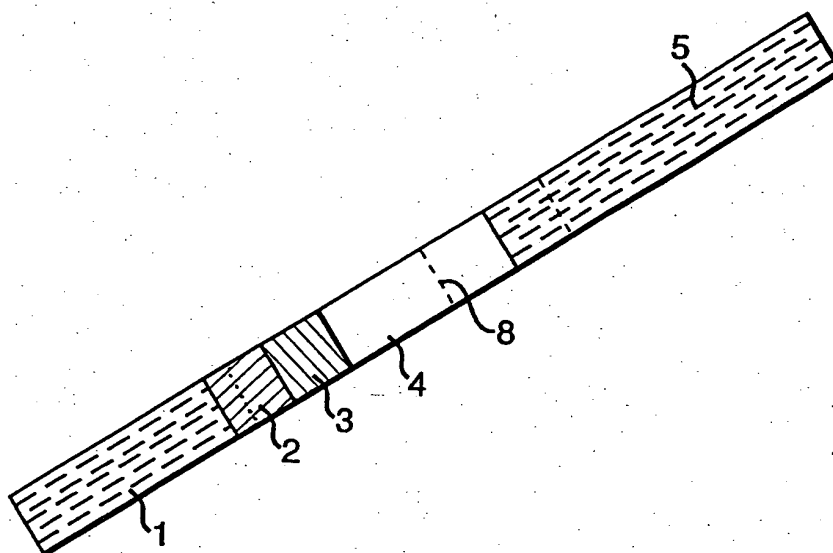
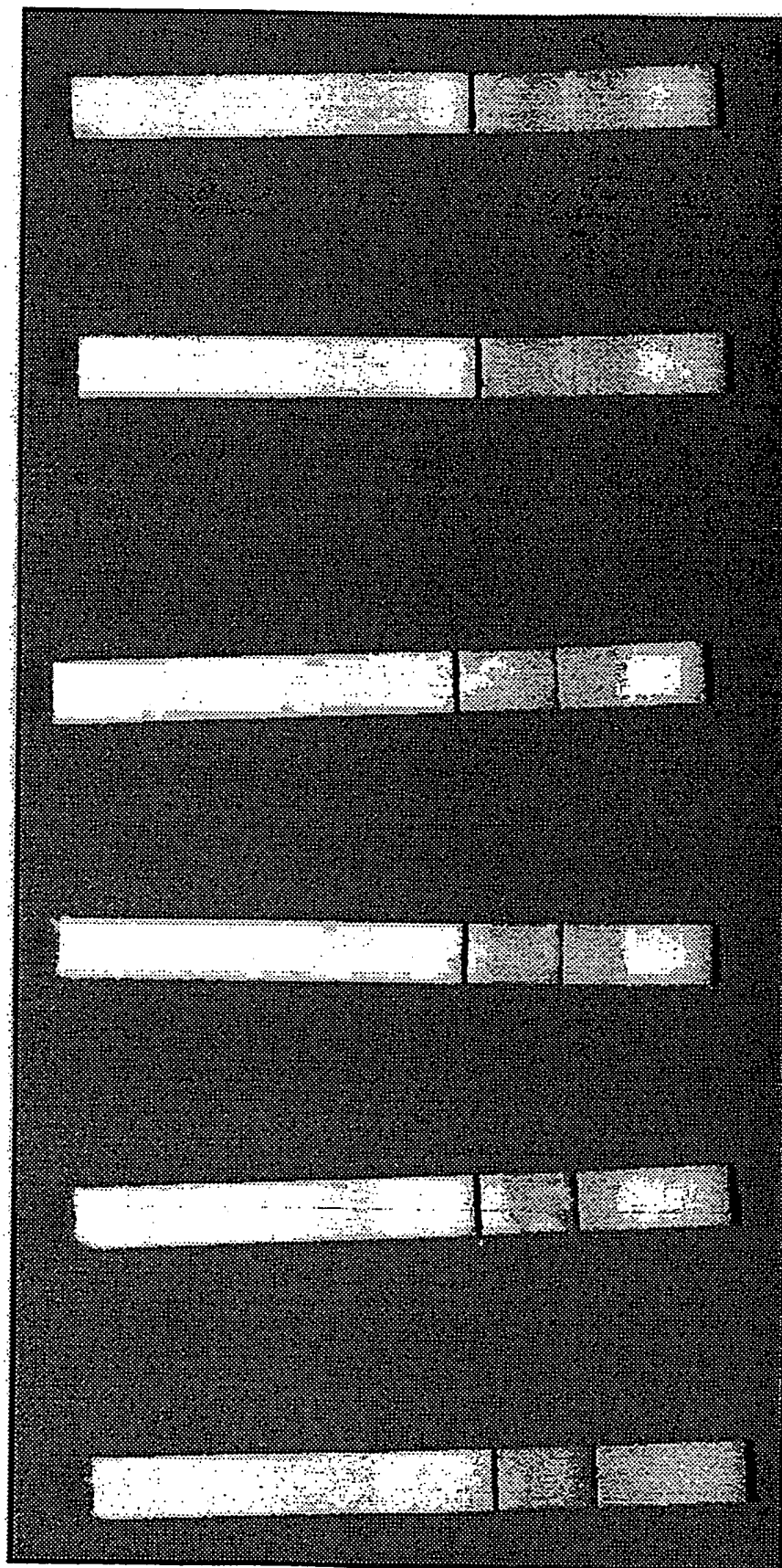


FIG. 1



2/2

FIG. 2



SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 99/03249

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/558 G01N33/543

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 387 696 A (ABBOTT LAB) 19 September 1990 (1990-09-19) claims 8-10 page 7, line 25 - line 58	1-13
X	EP 0 293 779 A (DAIICHI PURE CHEMICALS CO LTD) 7 December 1988 (1988-12-07) page 3, line 53 - page 4, line 5	1-13
X	WO 94 16329 A (ABBOTT LAB) 21 July 1994 (1994-07-21) claims page 5, line 3 - line 18 page 9, line 8 - line 26	1-13
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

*** Special categories of cited documents:**

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

15 February 2000

Date of mailing of the international search report

22/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2260 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 eponi,
Fax (+31-70) 340-3018

Authorized officer

Routledge, B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/03249

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 310 650 A (MCMAHON MICHAEL E ET AL) 10 May 1994 (1994-05-10) claims 1-6 column 4, line 22 -column 5, line 7 column 7, line 50 -column 8, line 27	1-13
A	EP 0 613 005 A (QUIDEL CORP) 31 August 1994 (1994-08-31) cited in the application claims 4-16 page 3, line 12 - line 18 page 6, line 14 - line 34 page 4, line 5 - line 27	1-13
A	WO 97 06439 A (QUIDEL CORP) 20 February 1997 (1997-02-20) cited in the application claims 13-23 page 4, line 18 - line 30 page 7, line 25 -page 8, line 28	1-13
A	US 5 741 662 A (BAUTISTA LORRAINE S ET AL) 21 April 1998 (1998-04-21) cited in the application claims column 3, line 13 - line 49 column 10, line 9 - line 67 column 14, line 26 -column 15, line 14	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/03249

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0387696 A	19-09-1990	AT 157404 T AU 636875 B AU 5119690 A CA 2012355 A DE 69031318 D JP 2283299 A US 5310650 A	15-09-1997 13-05-1993 20-09-1990 17-09-1990 02-10-1997 20-11-1990 10-05-1994
EP 0293779 A	07-12-1988	JP 63305251 A AT 71732 T DE 3867709 A US 4952520 A	13-12-1988 15-02-1992 27-02-1992 28-08-1990
WO 9416329 A	21-07-1994	AU 5994294 A	15-08-1994
US 5310650 A	10-05-1994	US 4960691 A AT 157404 T AU 636875 B AU 5119690 A CA 2012355 A DE 69031318 D EP 0387696 A JP 2283299 A AT 85130 T AU 598871 B AU 7903187 A CA 1303493 A DE 3783845 A EP 0262328 A JP 2086308 C JP 7036017 B JP 63096559 A	02-10-1990 15-09-1997 13-05-1993 20-09-1990 17-09-1990 02-10-1997 19-09-1990 20-11-1990 15-02-1993 05-07-1990 31-03-1988 16-06-1992 11-03-1993 06-04-1988 23-08-1996 19-04-1995 27-04-1988
EP 0613005 A	31-08-1994	US 5424193 A JP 6317591 A	13-06-1995 15-11-1994
WO 9706439 A	20-02-1997	AU 6720096 A	05-03-1997
US 5741662 A	21-04-1998	WO 9722714 A	26-06-1997